REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims remaining in this application be allowed.

Amendments

Claims 19-37 were pending in the present application. Claims 1-18 were previously withdrawn from consideration as drawn to a non-elected invention. By virtue of this response, claims 19-37 have been cancelled, without prejudice or disclaimer; and new claims 38-55 have been added. Accordingly, claims 38-55 are currently under consideration.

Concerning the priority claim

Enclosed for the Examiner convenience is a copy of the transmittal form submitted at the time of filing of this application. Please note that page 2 of this form claims 1-18 were canceled and on page 3 of this form a request to amend the first line of the specification to include the priority claim was entered.

Amendments

The claims in this application have been amended to reflect a method for enhancing the formation of a solid, non-migratory coherent mass at a selected vascular site of a mammal using a patentabley distinct composition. The composition used in the presently claimed method is the subject of U.S. Patent Application 09/574,379, filed on May 19, 2000, now issued U.S. Patent 6,531,111.

Specifically, Claim 38 corresponds to previously presented Claim 19 with the exception that this claim has been amended to recite a concentration range of biocompatible polymer "of from about 12 to about 50 weight percent," as supported by original Claim 2 and the specification at page 5, lines 5-6 and 15-16; page 6, lines 19-20; and page 11, lines 17-21.

Now presented Claim 39 corresponds to previously presented Claims 2 and 19 with similar concentration recitations as found in the specification at the specification at page 5, lines 5-6 and 15-16; page 6, lines 19-20; and page 11, lines 17-21.

Claims 40-55 correspond to previously presented Claims 20-25 and 28-37 respectively.

No new matter has been added.

Entry of these amendments is requested.

Rejection Under 35 U.S.C. §112, second paragraph

Claims 1-18 stand rejected under 35 U.S.C. §112, second paragraph, for the reasons noted of record in the Office Action. Applicants note that this rejection is moot in view of the fact that Claims 1-18 are not pending in this application.

As to now presented Claims 38-55, these claims recite "wherein the biocompatible polymer has a molecular weight and/or concentration sufficient to impart to the composition a viscosity of at least about 150 cSt at 40°C." Applicants maintain that these amendments render moot any application of this rejection against now presented Claims 38-55. However, in order to expedite prosecution, Applicants offer the following:

The viscosity recited in the claims by necessity refers to the composition comprising the polymer, the biocompatible solvent, and the contrast agent, as opposed to the precipitate formed therefrom. Specifically, the language of the rejected claims recites a composition comprising a biocompatible polymer, a biocompatible contrast agent, and a biocompatible solvent which "solublizes said biocompatible polymer". The claims later recite that this composition has the recited viscosity.

Contrarily, as is well known in the art (see, e.g., U.S. Patent No. 5,695,480), precipitation occurs when sufficient biocompatible solvent dissipates into the blood or other body fluid such that the polymer no longer is soluble in the resulting fluid environment. In such a case, the composition claim discussed above no longer applies since the biocompatible solvent no longer solubilizes the polymer.

Withdrawal of this rejection is requested.

Claim 2 stands rejected under 35 U.S.C. §112, second paragraph, as purportedly indefinite for failing to specify what the phrase "complete composition" refers to. As above, Claim 2 is not presented in this application and, accordingly, this rejection is moot.

Not to acquiesce in the Examiner's rejection, but solely to facilitate prosecution in the instant application, now presented Claim 38 does not employ the term "complete." Applicants maintain that this amendment does not limit the scope afforded by Claim 2 as one of ordinary skill in the art would recognize that "the complete composition" and "the composition" refer to the same entity. In light of the foregoing, withdrawal of this rejection is requested.

Rejections Under 35 U.S.C. §102/§103(a)

Claims 1-13 and 15-37 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by, or in the alternative, allegedly obvious under 35 U.S.C. § 103(a) by U.S. Patent No. 5,695,480 to Evans et al. ("Evans"). According to the Examiner, because the rejected claims are directed to compositions comprising a biocompatible polymer such as ethylene vinyl alcohol copolymer, a biocompatible contrast agent such as tantalum, and a biocompatible solvent such as dimethyl sulfoxide (DMSO), and because "Evans discloses compositions comprising ethylene vinyl alcohol copolymer in concentrations of 8 % weight, tantalum in concentrations of 30 % weight and DMSO in amounts of 100 ml (52-87.5 % weight) ... [and having a viscosity of] less than 60 centipoise at 20°C, " the rejected claims are anticipated. *Office Action, Pages 5-6.*[1] According to the Examiner, "[a]lthough Evans does not specifically recite the instantly claimed viscosity of 150 cSt at 40°C or migration distance, ... [the] compositions disclosed by Evans inherently possess the same viscosity and migration distance as the instantly claimed invention, because Evans' compositions comprise similar component[s] used in overlapping range[s] of concentrations as those claimed in the instant

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[1] Applicants respectfully wish to set forth the percentages contained in the Evans publication. Example 1 of the Evans publication references a first and a second composition. Both compositions contain 8 gm EVOH, 30 gm tantalum and 100 mL DMSO. The weight of the total composition is 8 gm+ 30 gm+ (100 mL x 1.1 gm/mL) =148 gm. Therefore, the weight percent, based on the total composition, of EVOH is about (8/148) = 5.4 %; of tantalum is about (30/148)= 20.3 %; and of DMSO is about (110/148) = 74.3 %. *See* Evans, Column 10, Lines 15-47. The compositions claimed in Evans include from about 2.5 to about 8.0 weight percent of a biocompatible polymer, from about 10 to about 40 weight percent of a water insoluble, biocompatible contrast agent, and from about 52 to about 87.5 weight percent of a biocompatible solvent. *See* Evans, Column 11, Claim 1. Similar to Evans, the weight percents listed for components in the compositions claimed in this application are listed based upon the total weight of the composition.

application.," The Examiner also maintains that the definitions of "kinematic viscosity" and "dynamic viscosity," as set forth in the Dictionary of Biochemistry and Molecular Biology, 2nd Edition, Stenesh, 1989 ("Stenesh"), clarify the asserted inherent characteristics that are silent in Evans. *Office Action, Page 6.*

In the alternative, the Examiner maintains that it would have been *prima facie* obvious to optimize the viscosity of the Evans formulation by routine experimentation. *Office Action, Page 7.*

Applicants respectfully traverse these rejections.

A. Background of the Art of the Invention

Before addressing the deficiencies of Evans and the other publications cited against the pending claims, Applicants believe a review of the art to which the instant invention belongs is in order.

Embolization of blood vessels is conducted for a variety of reasons, including the treatment of tumors, lesions (such as aneurysms), uncontrolled bleeding, and the like. Embolization as part of the treatment of aneurysms is preferably accomplished using catheter techniques that allow for the selective placement of the catheter in the aneurysmal sac. Recent advances now permit treatment of what would otherwise have been inoperable lesions.

However, embolization of aneurysms has presented distinct difficulties. For example, embolic compositions disclosed in the art comprised a biocompatible polymer, a biocompatible solvent, and a contrast agent. The contrast agent allowed for the visualization of the in vivo delivery of the composition via fluoroscopy. Visualization is particularly important when using catheter delivery techniques in order to ensure that not only that the composition is being delivered to the correct site, but also that the composition is being delivered in the correct amount. The problem arose with the visualization aspect of embolization that during the procedure, the physician lost the ability to visualize the composition. This, understandably, was a dangerous phenomenon that had to be remedied. The cited Evans publication (U.S. Patent No. 5,695,480) describes such a remedy.

Yet another phenomenon that arose in the art was that the typical embolization compositions[2] could migrate, solidify and form elongated, string-like masses distal from the point of ejection from the delivery catheter. That is, upon ejection of the composition in an aneursymal sac, the coherent mass subsequently formed was often distal, and not proximate, the ejection port of the syringe. This migration can result in embolization not at the aneurysmal sac, but at arteries attendant to the aneurysmal sac. Moreover, under high flow conditions, such formations could fragment, which can lead to incapacitation or death of the patient.

The art was unaware, at that time, of an effective way in which the migration and fragmentation problems could be avoided. **It was essential that the compositions comprised** no greater than 8 weight percent of biocompatible polymer because an amount any higher made the composition too viscous, and, therefore, too difficult to deliver using a syringe. One attempt at remedying the problem was to introduce a mechanical vaso-occlusive device, such as a metal coil, into the aneurysm (i.e., those described in U.S. Patent No. 6,335,384 to Evans et al.). This attempt is claimed to have the advantage of offering a longer-lasting embolization. However, such coils have a tendency to migrate. Migration away from the aneurismal cavity has been reported to result in distal embolization and regressive complete motor paralysis in patients. Migration within the aneurismal cavity prior to thrombosis can liberate calcified emboli from within the aneurysm cavity and cause intimal tears and vessel wall dissections. In addition, once placed in the aneurysm, the coils have been observed moving towards one another, or "packing." This results in a vacancy in the remainder of the aneurysm. The coils also have been observed moving out into the parent artery, which can lead to the embolization of the parent artery.

The present invention offers a novel and effective way to remedy these problems. That is, the claimed compositions are of a *high* viscosity that prevents fragmentation and allows for the formation of a solid, non-migratory mass having a substantially contiguous or "ball" shape. These high viscosity compositions permit more rapid and consistent **solidification in vivo**

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[2] Typical embolic compositions contain no more than 8 weight percent of biocompatible polymer, based on the weight of the total composition, and have a low viscosity which allows for easy administration of the composition via syringe. Compositions of this nature may be found in the cited publications: Greff I (US Patent No. 5,667,767), Taki, Greff II (US Patent No. 6,214,315), Greff III (U.S. Patent No. 5,580,568), Greff IV (US Patent No. 5,851,508), and Greff V (US Patent No. 6,051,607).

which renders migration from the ejection port of the catheter in the aneurysmal sac more difficult. Rapid and consistent solidification is important when embolizing because if not enough composition is delivered to the aneurysm, the patient is left with an active aneurysm; if too much composition is delivered, adjoining blood vessels may then embolize.

In the past, such high viscosity compositions would have been of no value because they would have been impossible to deliver via syringe and conventional catheter. The physician would have had to exert too strong a force on the plunger of the syringe, resulting in, if at all, the non-uniform and unpredictable delivery of the composition. The recent advent of delivery means which allow for effective delivery of high viscosity compositions, such as reinforced high-pressure microcatheters, threaded syringes, and screw syringes with force release mechanisms, make using the claimed high viscosity compositions practical.

Keeping in mind the state of the art prior to Applicants' discovery, as well as the nature of Applicants' discovery, is helpful when considering the following.

B. 35 U.S.C. § 102(b)

To anticipate a claim, a single **source must contain all of the elements of the claim.** *Hybritech Inc. v. Monoclonal Antibodies, Inc,, 802* F.2d *1367, 1379* (Fed. Cir. *1986).* Claims 38-55 each contain the requirement that viscosity of the composition be at least about 150 cSt at 40°C. Therefore, for Evans to anticipate these claims, it must contain Applicants' viscosity element. It does not.

The Evans publication is directed to the problem observed in field that during catheter delivery of embolic compositions having average particle sizes of greater than 10 μm, a portion of the contrast agent was not maintained in the embolic composition. *See Evans, Column 3, lines 15-18.* This created an expressly dangerous situation, as discussed above, because the physician was not able to consistently visualize delivery of the composition to the vascular site, and, therefore, could either under or over filled the vascular site. Failure to fill the site completely results in an active aneurysm. *See Evans, Column 2, Lines 33-36.* Over filling the site results in the composition flowing into the adjoining blood vessels, which can cause distal embolization and ischemia.

To remedy this visualization problem, Evans employed water insoluble contrast

agents whose average particle size is about *10 μm or* less. *See Evans, Column 3, Lines 6*-14. The only information that Evans contains regarding viscosity relates to the ability to adjust the viscosity of the composition as needed for catheter delivery by adjusting the molecular weight of the polymer used. *See, e.g., Evans, Column* 5, *Lines* 43-50. Recall, catheter delivery at the time of Evans' invention did not include the reinforced high pressure microcatheters, threaded syringes or screw syringes with force release mechanisms discussed above. Accordingly, the compositions of Evans had to be of low enough viscosity such that they could be delivered with then conventional catheter technology. Because such low viscosity compositions are the antithesis of Applicants' high viscosity compositions, Applicants submit that Evans does not contain every element of Applicants' invention.

The Examiner admits that Evans is silent as to the claimed viscosity of at least about 150 cSt at 40°C. However, the Examiner takes the position that the "compositions disclosed by Evans inherently possess the same viscosity and migration distance as the instantly claimed invention, because Evans' compositions comprise similar component[s] used in overlapping range[s]. " Office *Action, Page 6*. That is, according to the Examiner, even though Evans uses units of centipoise and Applicants use units of centistokes, the Evans compositions, once converted into the same units, possess the same viscosities as the compositions claimed by Applicants.

Applicants submit that none of the compositions in Evans contains the requirement that the composition possess a viscosity of at least about 150 cSt at 40°C. As demonstrated below, the viscosities recited in Evans, when converted from centipoise to centistokes do not meet the claimed recitation of at least about 150 cSt at 40°C. The above is confirmed by the fact that the delivery techniques employed at the time of Evans' invention only allowed for the delivery of low viscosity compositions. High viscosity compositions were **simply impossible or too difficult to deliver using the delivery techniques** of **the time.**

Moreover, Applicants have amended the claims to include the requirement that "the biocompatible polymer has a molecular weight and/or concentration sufficient to impart to the composition a viscosity of at least about 150 cSt at 40°C. "

In addition to the above, the claims in this application have now been amended to recite that the concentration of the biocompatible polymer is from about 12 to about 50 weight percent.

Such a recitation clearly distinguishes over the cited publications and, accordingly, these rejections are now moot.

In summary, because every limitation contained within Claims 38-55 is not disclosed, Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejections over Evans.

C. 35 U.S.C. § 103(a)

When applying 35 U.S.C. § 103(a), four tenets of patent law must be adhered to: (1) the claimed invention must be considered as a whole, (2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination, (3) the references must be viewed without the benefit of impermissible hindsight vision, and (4) a reasonable expectation of success is the standard with which obviousness is determined. *See MPEP § 2141,* citing *Hodosh v. Block Drug Co., Inc.,* 786 F.2d 1136, 1143 (Fed. Cir. 1986). Moreover, to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or to combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See MPEP § 2142.* Applicants respectfully assert that these tests of obviousness have not been met in this case.

Applicants maintain that a prima *facie* case of obviousness has not been established because there is no suggestion or motivation, outside Applicants' own disclosure, to modify the Evans publication to arrive at Applicants' claimed invention. As indicated above, the invention described in Evans is directed to maintaining visualization of the composition as it is delivered to the vascular site so that the physician delivers the appropriate amount of composition. To obtain this objective, Evans relies upon an average particle size for the water insoluble contrast agent of about 10 μm or less. Evans describes using its particular contrast agents in compositions having low viscosities because at the time, there was no way to effectively deliver *high* viscosity compositions. Therefore, one of skill in the art would not have been motivated to alter the viscosity of the composition because if he did, such an alteration would have rendered the composition undeliverable.

Moreover, the limitations imposed by conventional syringe techniques is the second reason why a prima *facie* case of obviousness has not been made out - that is, one of skill in the

art would not **have had** a reasonable expectation of success in arriving at an effective embolizing composition when such high-viscosity compositions were **impossible to deliver.**

Because Evans provides no suggestion or motivation to alter the viscosity of its compositions, because one would not have had a reasonable expectation of success in arriving at an effective embolizing composition, and because Evans does not contain every element of Applicants' invention, Applicants submit that a *prima facie* case of obviousness has not been made out and respectfully request withdrawal of the 35 U.S.C. § 103(a) rejection over Evans.

Assuming, for discussion only, that a *prima facie* case of obviousness has been made out, Applicants submit that the unexpected and surprising results obtained with the instant invention nullify such a case. As indicated in the Declaration of Thomas J. Whalen II, submitted in the parent to this case and a copy of which is attached, it was unexpected and surprising that Applicants' high viscosity compositions were less prone to the fragmentation that occurred with embolic compositions prior to Applicants' compositions. It was also unexpected and surprising that Applicants' *high viscosity* compositions formed solid masses of significantly reduced migration and that Applicants' *high viscosity* compositions did not migrate out of the aneurysmal sac.[3]

In addition to the above, the claims in this application have now been amended to recite that the concentration of the biocompatible polymer is from about 12 to about 50 weight percent. Such a recitation clearly distinguishes over the cited publications and, accordingly, these rejections are now moot.

In summary, Applicants maintain that a prima *facie* case of obviousness has not been made out against the instant invention. In the alternative, Applicants maintain that the experimental data contained within the Specification and/or the Declaration of Mr. Whalen confirm the surprising and unexpected results which render moot the obviousness inquiry. In light of the foregoing, Applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) rejection over Evans.

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[3] Applicants maintain that the Declaration of Thomas J. Whalen II, submitted herewith, sufficiently addresses the surprising and unexpected nature of the claimed invention and that the

3. Rejections Over Greff

Claims 1-37 stand rejected under 35 U.S.C. §102(b)/§103(a) as allegedly anticipated by, or in the alternative, obvious over U.S. Patent No. 5,667,767 to Greff, et al. ("Greff I"). According to the Examiner, Greff I anticipates Claims 1-37 because it "discloses embolizing compositions comprising ethylene vinyl alcohol copolymers at a concentration of 5.8 and 6.8 % weight, tantalum at concentrations of 10 % weight, and DMSO at concentrations of about 52 % to about 87.5 % weight ... [and] the use of a water soluble contrast agent such as metrizamide at concentrations of 38.5 % weight." *Office Action, Page 8.* In the alternative, the Examiner maintains that it would have been *prima facie* obvious to optimize the viscosity range of Greff's composition by routine experimentation to arrive at Applicants' invention. *Office Action, Page 8.*

Applicants respectfully traverse these rejections.

A. 35 U.S.C. § 102(b)

As indicated above, to anticipate a claim, a single source must contain all of the elements of the rejected claim. *Hybritech,* 802 F.2d at 1369. Greff I does not possess Applicants' element of a viscosity of at least about 150 cSt at 40°C. Accordingly, Greff I does not anticipate Claims 1-37. 1

Greff I is, instead, directed to the discovery that various embolizing and contrasting agents may or may not be suitable, when combined together, for embolization. This is because a successful combination of embolizing agent and contrast agent requires compatibility between these components in producing the requisite **coherent precipitate** having the contrast agent encapsulated therein as well as maintaining the requisite properties for vascular use. *See Greff I, Column* 2, *Lines 54-67.* The invention of Greff I is directed to compositions comprising an ethylene vinyl alcohol copolymer dissolved in a biocompatible solvent and a water insoluble contrast agent selected from either tantalum, tantalum oxide, or barium sulfate. *See Greff I, Column 3, Lines 5-9.* Greff I states that embolization compositions, ideally, should be easy to deliver (e.g., low viscosity) and that the claimed composition preferably has "a viscosity equal to or less than 60 centipoise at *20°C. " Greff I, Column 1, Lines* 51-52; *Column 4, Lines 40-44.*

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data of Example 3 is deemed not necessary and, accordingly, is not relied on herein. Applicants reserve the right to rely upon the data of Example 3 in the future.

As is known in the art, one centipoise (cP) equals kinematic viscosity (in centistokes) multiplied by density (in gm/cc). Correspondingly, one centistoke (cSt) is equal to viscosity (in centipose) divided by the density (in gm/cc). The density of the solvent in this instance is about 1.10. The density of the solution is about the same. Additionally, tantalum has no effect on the viscosity of the solution. Therefore, in units of centipoise (cP), the compositions of the claimed methods of the instant invention would have an absolute viscosity of approximately 165 cP.

Thus, the viscosity of the polymer compositions taught by Greff I (i.e., 60 cP, or 54.5 cSt at 20°C)[4] is about three-fold less than the viscosity of the polymer compositions of Applicants' claims (i.e., 165 cP, or 150 cSt at 40°C). Certainly, these compositions are not the same as the highly viscous compositions of Applicants' claimed methods ("at least 150 cSt at 40°C").

Because Greff I does not disclose Applicants' compositions having a viscosity of at least about 150 cSt at 40°C, Greff I does not anticipate Applicants' claims.

In addition to the above, the claims in this application have now been amended to recite that the concentration of the biocompatible polymer is from about 12 to about 50 weight percent. Such a recitation clearly distinguishes over the cited publication and, accordingly, these rejections are now moot.

Accordingly, Applicants respectfully request that the 35 U.S.C. § 102(b) rejections to Claims 1-37 over Greff I be withdrawn.

B. 35 U.S.C. § 103(a)

The test for establishing a prima facie case of obviousness is set forth above. Applicants believe that none of the test prongs has been satisfied. As discussed above, compositions of Greff I preferably have viscosities *equal to or less than 60* centipoise at 20°C. Such compositions would have an even *lower viscosity* at Applicants' temperature of 40°C. Greff I indicates that such a low viscosity is desirable because it makes the composition "easy to

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[4] Like Evans, Greff I lists viscosities of about 60 centipoise at 20°C (which is about 40 cSt or less at 40°C). Applicants list viscosities at 40°C. It is art accepted that the viscosity of a composition decreases as temperature increases. Therefore, not only are the absolute viscosity measurements of Applicants' compositions different than the cited publications, but once temperature is considered, the viscosities are even further removed from one another.

deliver." *See Greff I Column 1, Lines* 51-52. Therefore, one of skill in the art, armed with the disclosure of Greff I and the practical limitation that no delivery means could at that time deliver a high-viscosity composition, would not have been motivated to violate the low-viscosity parameter discussed therein and would not have expected to achieve a successful embolic composition. These truths, coupled with the fact that the cited compositions do not possess Applicants' claimed viscosities, demonstrate that the elements of the *prima facie* case of obviousness have not been proven. Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) rejection to Claims 1-37 over Greff I.

In the alternative, if a *prima facie* case of obviousness is found to exist, Applicants assert that the unexpected nature of Applicants' compositions rebuts such an obviousness determination. Applicants rely on the Declaration of Mr. Whalen submitted in the parent application.

In addition to the above, the claims in this application have now been amended to recite that the concentration of the biocompatible polymer is from about 12 to about 50 weight percent. Such a recitation clearly distinguishes over the cited publication and, accordingly, these rejections are now moot.

Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) rejections to Claims 1-37 over Greff **1.**

4. Reiection Over Taki et al.

Claims 1-6, 9-10 and 14-37 stand rejected under 35 U.S.C. § 102(b)/§ 103(a) as allegedly anticipated by, or in the alternative, obvious over *"A New Liquid Material for Embolization ofArteriovenous Malformations"* to Taki et al. ("Taki"). According to the Examiner, because Taki discloses compositions comprising ethylene vinyl alcohol copolymer at a concentration of 5 % weight, metrizamide at concentrations of 35 % weight, and DMSO at concentrations of about 60% weight, the rejected claims are anticipated. According to the Examiner, " [a]lthough Taki does not explicitly disclose the instantly claimed viscosity of 150 cSt at 40°C or the migration distance, using the same analogy as discussed above, ... Taki inherently possesses the same viscosity and migration distance as the instantly claimed invention ...

In the alternative, the Examiner maintains that it would have been prima *facie* obvious to optimize the viscosity range of Taki's composition by routine experimentation.

Applicants respectfully traverse these rejections.

A. 35 U.S.C. § 102(b)

The test for anticipation is discussed above. As with Evans and Greff I, Taki fails the anticipation test because it does not disclose Applicants' composition viscosity of at least about 150 cSt at 40°C. Instead, Taki, discloses a classic low-viscosity embolization composition, detailed above in the summary of the art, that contains no more than eight weight percent of biocompatible polymer so that the resulting composition is easy to deliver via syringe. Because Taki does not disclose all of the elements of Applicants' Claims 1-6, 9-10, and 14-37, Applicants respectfully request withdrawal of the 35 U.S.C, § 102(b) rejections over Taki.

B. 35 U.S.C. § 103(a)

Taki does not provide the requisite suggestion or motivation to modify the viscosity of Taki to Applicants' viscosity of at least about 150 cSt at 40°C. In addition, as with Greff I, one of skill in the art would not have had a reasonable expectation of achieving a successful embolization composition if he somehow were motivated to elevate the viscosity because he would have had no means to deliver such a composition. Those deficiencies and Taki's failure to contain Applicants' viscosity shows that a prima *facie* case of obviousness has not been made out. Applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) rejections against Claims 1-6, 9-10, and 14-37.

In the alternative, if a prima *facie* case of obviousness is found to exist, Applicants assert that the unexpected nature of Applicants' compositions rebuts such an obviousness determination. Applicants rely on the Declaration of Mr. Whalen submitted from the parent application.

In addition to the above, the claims in this application have now been amended to recite that the concentration of the biocompatible polymer is from about 12 to about 50 weight percent. Such a recitation clearly distinguishes over the cited publication and, accordingly, these rejections are now moot.

Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) rejections to Claims 1-37 over Taki.

5. Rejections Over Greff II

Claims 1-6 and 9-17 stand rejected under 35 U.S.C. § 102(e)/§ 103(a) as allegedly anticipated by, or in the alternative, obvious over U.S. Patent No. 6,214,315 B1 to Greff et al. ("Greff II"). According to the Examiner, Greff II anticipates Claims 1-6 and 9-17 because it discloses compositions comprising ethylene vinyl alcohol copolymers at a concentration of about 5 % weight, tantalum at concentrations of 14 % weight, DMSO at concentrations of about 74% weight, and iridium powder at concentrations of about 6% weight.[5]

In the alternative, the Examiner maintains that it would have been prima *facie* obvious to optimize the viscosity range of Greff II by routine experimentation, thus obtaining the optimal range of viscosity for the safest and most effective clinical outcome.

Applicants respectfully traverse these rejections.

A. 35 U.S.C. § 102(e)

Greff II does not contain the composition viscosity "of at least about 150 cSt at 40°C" element that Applicants' Claims 1-6 and 9-17 do. Accordingly, Greff II does not anticipate Claims 1-6 and 9-17. Moreover, Claims 1-17 are not in this application.

Greff II is directed to embolic compositions comprising radioactive agents which are delivered to the vascular site as a fluid and which then solidify *in vivo* to form a solid, coherent mass. *See Greff II, Column 3, Lines 32-35.* The solid, coherent mass aspect of Greff II's compositions was an advance in the art because, *inter alia,* chemotherapeutic

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[5] Applicants respectfully wish to set forth the percentages contained in the Greff II publication. Example I of the Greff II publication references a composition containing 0.396 gm EVOH, 1.485 gm tantalum and 4.95 mL DMSO. The weight of the total composition is 0.396 gm + 1.485 gm + (4.95 mL x 1.1 gm/mL) = 7.326 gm. Therefore, the weight percent, based on the total composition, of EVOH is about (0.396/7.326) = 5.4 %; of tantalum is about (1.285/7.326) = 20.3 %; and of DMSO is about (5.445/7.326) =74.3 %. *See* Greff II, Column 12, Lines 44-50. Similar to Greff II, the weight percents listed for components in the compositions claimed in this application are listed based upon the total weight of the composition.

agents before those claimed were susceptible to migration and systemic delivery *in vivo* with potential side effects in the patient. *See Greff II, Column 3, Lines 23-25.*

Greff II is silent as to viscosity of the compositions. Because Greff II *cannot* be relied on for elements *not* taught or suggested therein, Greff II does not anticipate Claims 1-6 and 9-17.

In addition to the above, the claims in this application have now been amended to recite that the concentration of the biocompatible polymer is from about 12 to about 50 weight percent. Such a recitation clearly distinguishes over the cited publication and, accordingly, these rejections are now moot.

Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. § 102(e) rejections to these claims based on Greff II.

B. 35 U.S.C. § 103(a)

Applicants submit that Greff II suffers from the same deficiencies as Evans, Greff I, and Taki, discussed above. In sum, Greff II fails to suggest to or motivate one of skill in the art to modify the viscosity of the embolic composition to at least about 150 cSt at 40°C. Greff II also fails to provide one of skill in the art a reasonable expectation of arriving at a successful embolization composition with a viscosity of at least about 150 cSt at 40°C and does not provide all limitations of Applicants' claims. Accordingly, Applicants believe that a prima facie case of obviousness has not been made out, and that the 35 U.S.C. § 103(a) rejections to Claims 1-6 and 9-17 should be withdrawn.

In the alternative, if a prima facie case of obviousness is found to exist, Applicants assert that the unexpected nature of Applicants' compositions rebuts such an obviousness determination. Applicants rely on the Declaration of Mr. Whalen submitted in the parent application.

In addition to the above, the claims in this application have now been amended to recite that the concentration of the biocompatible polymer is from about 12 to about 50 weight percent. Such a recitation clearly distinguishes over the cited publication and, accordingly, these rejections are now moot.

Accordingly, Applicants respectfully request withdrawal of the 35 U.S.C. § 103(a) rejection to Claims 1-17 over Greff II.

6. Rejections Under Obviousness-Type Double Patenting

Claims 1-37 stand rejected under the judicially-created doctrine of obviousness-type double patenting as purportedly unpatentable over: Claims 1-5 of U.S. Patent No. 5,580,568 to Greff et al. ("Greff III"); Claims 1-43 of U.S. Patent No. 5,695,480 to Evans et al. ("Evans"); Claims 1-15 of U.S. Patent No. 5,851,508 to Greff et al. ("Greff IV"); Claims 1-15 of U.S. Patent No. 5,667,767 to Greff et al. ("Greff F); Claims 1-17 of U.S. Patent No. 6,051,607 to Greff ("Greff V"); and Claims 1-21 of U.S. Patent No. 6,214,315 to Greff et al. ("Greff II"); Claims 1-20 of U.S. Patent No. 6,454,738 and Claims 1-15 of U.S. Patent No. 6,531,111. According to the Examiner, although the conflicting claims are not identical, "they are not patentably distinct from each other because both the patented claims and the instant pending claims are directed to compositions comprising a biocompatible polymer, a biocompatible contrast agent and a biocompatible solvent." Applicants respectfully traverse these rejections.

A double patenting rejection of the obviousness-type is analagous to a failure to meet the nonobviousness requirement of 35 U.S.C. § 103, except that the patent principally underlying the double patenting rejection is not considered prior art. *M.P.E.P. §* 804(I&B)(1). Since the analysis employed in an obviousness-type double patenting determination parallels the guidelines for a 35 U.S.C. § 103(a) rejection, the factual inquiries set forth in *Graham v. John Deere Co.* are employed when making an obviousness-type double patenting analysis. Id. These factual inquiries require that one: (A) determine the scope and content of a patent claim and the prior art relative to a claim in the application at issue; (B) determine the differences between the scope and content of the patent claim and prior art as determined,in (A) and the claim in die application at issue; (C) determine the level of ordinary skill in the pertinent art; and (D) evaluate any objective indicia of nonobviousness. Id. It is important to recall that "[w]hen considering whether the invention

defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art." Id.

None of the cited patents except Whalen II, U.S. Patent No. 6,531,111 and Tran, et al., U.S. Patent No. 6,454,738, disclose embolic compositions as per this invention and, accordingly, the obviousness type double patenting rejections over these remaining references is in error.

As to Whalen II, this patent is the parent of the present application and is directed solely to composition claims which were restricted from the now prosecuted method claims. Hence, a double patent rejection is in error over this reference.

Lastly, while not acquiescing in the rejection over Tran, et al., Applicants will submit in due course a terminal disclaimer to obviate this rejection.

Withdrawal of this rejection is requested.

CONCLUSION

Applicants have made a sincere effort to overcome the rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

Respectfully submitted,

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By 

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